## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Prescribing Pattern of Antipsychotic Medication for First Episode Psychosis: A Retrospective Cohort Study |
| **AUTHORS** | Keating, Dolores; McWilliams, Stephen; Boland, Fiona; Doyle, Roisin; Behan, Caragh; Strawbridge, Judith; Clarke, Mary |

## VERSION 1 – REVIEW

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| **REVIEWER** | Farooq, Saeed<br>Keele University, Psychiatry |
| **REVIEW RETURNED** | 17-Aug-2020 |

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| **GENERAL COMMENTS** | **Review of ''Prescribing Pattern of Antipsychotic Medication for First Episode Psychosis: A Retrospective Cohort Study.**<br><br>This is interesting study and can be recommended for publication. It will need some improvement as suggested below:<br><br>1. Aims need to be clearly described. The abstract states that 'This study assess the influence of guidelines on clinical practice'. While in the introduction it states 'In this study we describe the pattern of antipsychotic medication use in two cohorts of FEP<br>patients before and after the introduction of an EIP service in the context of evolving clinical practice guidelines.' I think latter is better reflection of the study, it only describes the pattern of antipsychotics prescription. The influence of guidelines is one of the many reasons for prescribing pattern. Moreover study does not directly assess the effect of guidelines.<br>2. Authors need to give more details of how data was collected. What is 'business intelligence' (line 19, page 9). Please give more details.<br><br>3. While study describes prescribing patterns, it is too narrowly focussed on Olanzapine. I agree that Olanzapine stands out due to its mention in guidelines, but there are other guidelines pertaining to drug used in FEP. These need to be considered. I did not find any mention of Clozapine. Was it not prescribed or excluded from analysis. Clozapine has been used in FEP sometimes with good effect (e.g Agid et al, 2007) and I think authors need to comment on it and overall adherence with guidelines.<br><br>4. Authors need to discuss other reasons for the prescription patterns and also need to take into account the differences in their two cohorts. For example, C-1 had far higher |

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| | prevalence of schizophrenia compared to C-2 (59%vs 39%). Similarly, substance induced psychotics disorders were almost twice more common in C2 compared to C-1. Not sure this statistically significant but the prescribing patterns would differ by diagnosis as well.<br><br>5. Some of the tables could be removed and only relevant information could be given in text. For example, I am not clear what is purpose of table 4 giving the baseline demographic and clinical characteristics of patients who require switching. I am nalos not clear why the switching data is described in such detail, when the reasons for switching are not clear. In essence the data tells us the drug A was switched to drug B. The reasons for switching vary, lack of efficacy or tolerability being the most common. It is not clear in methods whether authors examined the reasons for switching or they are just assuming it was lack of tolerability or efficacy.<br><br>6. They take an arbitrary cut off points for describing the low, medium and high dose. While high dose prescribing is clearly defined in literature, low and medium are not, Authors need to describe the assumptions on which low and medium doses. These can be described but we need to be clear what are the basis for these since lot of results are based on these cut offs.<br><br>7. The discussion needs revision and improvement. At present this reads more like a literature overview with no meaningful comparisons and inferences. In particular authors need to consider other reasons for prescription patterns (e.g. time trends, inadequate support (?) from services requiring prescription of drugs like olanzapine, lack of alternatives as some would argue quetiapine and aripiprazole have their own problems). In particular, pharmacological guidance for FEP need to be considered as a whole in discussing the findings.<br><br>**8. Reference**<br>Agid O, Remington G, Kapur S, Arenovich T, Zipursky RB. Early use of clozapine for poorly responding first-episode psychosis. *J Clin Psychopharmacol*. 2007;27(4):369-373. doi:10.1097/jcp.0b013e3180d0a6d4 |

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| **REVIEWER** | Swapna Verma<br>Institute of Mental Health<br>Singapore |
| **REVIEW RETURNED** | 09-Sep-2020 |

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| **GENERAL COMMENTS** | This is a descriptive study looking at prescription patterns of antipsychotic medication in patients with first-episode psychosis over a span of 20 years. The notable results were the increase in prescription for SGAs between the 1st and 2nd cohort, use of low doses in majority of the cases, and the high use of olanzapine. .<br><br>The change in prescription pattern between cohort 1 and 2 was more likely to be an effect of time rather than introduction of EIP |

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| | services. Also, there was not enough data on patient characteristics (like BMI, patient preferences) to conclude that patient characteristics did not affect choice of antipsychotic medication.<br><br>Authors should have used regression analyses to look at factors associated with olanzapine use and prescription of high doses as compared to low doses.<br><br>Tables 3, 4 and 5 in the paper were not necessary at all.<br><br>Overall, the findings of the study were not novel, at best this could be re-written as a brief report. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

1. Aims need to be clearly described. The abstract states that 'This study assess the influence of guidelines on clinical practice'. While in the introduction it states 'In this study we describe the pattern of antipsychotic medication use in two cohorts of FEP patients before and after the introduction of an EIP service in the context of evolving clinical practice guidelines.' I think latter is better reflection of the study, it only describes the pattern of antipsychotics prescription. The influence of guidelines is one of the many reasons for prescribing pattern. Moreover study does not directly assess the effect of guidelines.
Thank you. We have updated the abstract to reflect the aims of the study in a clearer way as suggested.
2. Authors need to give more details of how data was collected. What is 'business intelligence' (line 19, page 9). Please give more details.
The electronic health record used by the services is called the Mental Health Information System (MHIS). While this system allows for the creation of prescriptions, it does not have an in-built reporting system to generate the data required for the study. The organisation uses separate software called Discoverer Plus, which is a business intelligence software meaning it can be used to extract data from our electronic health record in order to generate reports. In this case the programme was run using the data elements relevant to the study and extracted the relevant prescribing data from the EHR. The methodology has been updated with more detail.
3. While study describes prescribing patterns, it is too narrowly focussed on Olanzapine. I agree that Olanzapine stands out due to its mention in guidelines, but there are other guidelines pertaining to drug used in FEP. These need to be considered.
Thank you. We have reviewed the paper in general in order to reduce the focus on olanzapine as suggested. We have previously conducted a systematic review of guidelines for the treatment of schizophrenia and updated the review to consider revised guidelines from the British Association for Psychopharmacology and the guidelines from the American Psychiatric Association published in September 2020. We have restructured the discussion in light of this review.

4. I did not find any mention of Clozapine. Was it not prescribed or excluded from analysis. Clozapine has been used in FEP sometimes with good effect (e.g Agid et al, 2007) and I think authors need to comment on it and overall adherence with guidelines.
Thank you for this observation and we have now included comments on clozapine use in the paper. Clozapine was not excluded but it had not yet been prescribed for anyone in this cohort. This is likely because patients had less than 30 days exposure to antipsychotic treatment prior to contact with the services. We have added previously published data on clozapine use in these cohorts.

5. Authors need to discuss other reasons for the prescription patterns and also need to take into account the differences in their two cohorts. For example, C-1 had far higher prevalence of schizophrenia compared to C-2 (59%vs 39%). Similarly, substance induced psychotics disorders were almost twice more common in C2 compared to C1. Not sure this statistically significant but the prescribing patterns would differ by diagnosis as well.
A section of the paper discussing prescribing patterns in the two cohort has been revised to include more discussion regarding the reasons for prescribing patterns. The DUP for cohort 2 was significantly reduced meaning many of those presenting for care would not yet fulfil criteria for schizophrenia. As many were comorbid substance misusers, some of those diagnosed initially with substance induced psychosis may subsequently convert to a schizophrenia diagnosis.
6. Some of the tables could be removed and only relevant information could be given in text. For example, I am not clear what is purpose of table 4 giving the baseline demographic and clinical characteristics of patients who require switching. I am also not clear why the switching data is described in such detail, when the reasons for switching are not clear. In essence the data tells us the drug A was switched to drug B. The reasons for switching vary, lack of efficacy or tolerability being the most common. It is not clear in methods whether authors examined the reasons for switching or they are just assuming it was lack of tolerability or efficacy.
Thank you. We have removed table 4. It is a limitation of the study that we don't have data on the reasons for switching medication and we have added this to the relevant section of the paper.
7. They take an arbitrary cut off points for describing the low, medium and high dose. While high dose prescribing is clearly defined in literature, low and medium are not. Authors need to describe the assumptions on which low and medium doses. These can be described but we need to be clear what are the basis for these since lot of results are based on these cut offs.
A comparison of pharmacological treatment guidelines found that while 'low doses' or 'doses at the lower end of the range' than for multi-episode schizophrenia are frequently recommended, the actual doses are not clearly defined in many guidelines. Studies such as EUFEST give some indication of effective doses for FEP. Using current research and guidelines we decided on a pragmatic approach to defining 'doses at the lower end of the dose range' as being < 50% of the maximum BNF dose.

8. The discussion needs revision and improvement. At present this reads more like a literature overview with no meaningful comparisons and inferences. In particular authors need to consider other reasons for prescription patterns (e.g. time trends, inadequate support (?) from services requiring prescription of drugs like olanzapine, lack of alternatives as some would argue quetiapine and aripiprazole have their own problems). In particular, pharmacological guidance for FEP need to be considered as a whole in discussing the findings.
As suggested, the discussion has been revised. Thank you.
9. Reference
Agid O, Remington G, Kapur S, Arenovich T, Zipursky RB. Early use of clozapine for poorly responding first-episode psychosis. J Clin Psychopharmacol. 2007;27(4):369-373. doi:10.1097/jcp.0b013e3180d0a6d4
Thank you. This reference has been included in the paper.

Reviewer: 2

Please leave your comments for the authors below
This is a descriptive study looking at prescription patterns of antipsychotic medication in patients with first-episode psychosis over a span of 20 years. The notable results were the increase in prescription for SGAs between the 1st and 2nd cohort, use of low doses in majority of the cases, and the high use of olanzapine. .

1. The change in prescription pattern between cohort 1 and 2 was more likely to be an effect of time rather than introduction of EIP services.
Yes, thank you. We have clarified this in the paper.
2. Also, there was not enough data on patient characteristics (like BMI, patient preferences) to conclude that patient characteristics did not affect choice of antipsychotic medication.
Thank you for comment. We have clarified that we did not find evidence that the patient factors we investigated had a significant impact on choice or dose of antipsychotic medication in this cohort. The impact of other factors on choice and dose of antipsychotic has been discussed.
3. Authors should have used regression analyses to look at factors associated with olanzapine use and prescription of high doses as compared to low doses.
Thank you. We conducted regression analysis as suggested.
4. Tables 3, 4 and 5 in the paper were not necessary at all.
Thank you, the tables have been removed.
Overall, the findings of the study were not novel at best this could be re-written as a brief report.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Farooq, Saeed<br>Keele University, Psychiatry |
| **REVIEW RETURNED** | 10-Dec-2020 |

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| **GENERAL COMMENTS** | Authors have responded to comments satisfactorily |